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14. ABSTRACT The etiology of blast-induced traumatic brain injury (bTBI) is largely undefined. Along with reducing mortality, in preliminary experiments Kevlar vests significantly protected against bTBI in rats. We postulate that: 1) blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature that elicit intracranial disruptions, and 2) Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast. Using a compression driven shock tube, we compare external, systemic (e.g. vascular), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. We seek to: 1) determine if measured pressure changes are blast severity-dependent and correspond with outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures and establish whether a protective vest encasing the thorax ameliorates blast-induced brain injury, pointing to a contribution of the effects of blast on the thorax to brain injury. These studies will provide insights into the etiology of blast-induced brain injury and will advance the development of mitigation strategies.					
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INTRODUCTION

Body armor has made blast injuries survivable; consequently, we speculate that to a large extent blast-induced head injuries have emerged among troops who without body armor would have simply been killed in action as a result of injury to more vulnerable organs such as the lung. Serendipitously, in a preliminary experiment we noted that along with reducing mortality, lung injury, and cardiovascular disruptions by blast overpressure (BOP), Kevlar vests protected against BOP-induced neuropathological changes in rats. These preliminary findings suggested that a protective vest encasing the thorax might ameliorate blast-induced brain injury, pointing to a significant contribution of the effects of blast on the thorax to brain injury pathophysiology. We hypothesize that much of the blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature (venous as well as arterial) that elicit a series of intracranial disruptions, and that Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast.

To address how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain, we have attempted to measure, compare, and correlate external, systemic (e.g. vascular arterial and venous), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. In particular, in the work completed to date, we used a compression driven shock tube to: 1) determine if measured pressure changes are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures. As detailed below, in addition to neuropathological and neurobehavioral evaluations, these outcome measures have included assessments of blood-brain barrier integrity and cerebral blood flow measurements, since we postulate that the cerebrovasculature plays a pivotal role in blast-induced brain injury pathophysiology, and is likely to be disrupted by blast-induced perturbations.

BODY

Research accomplishments associated with each task outlined in the approved Statement of Work are described below.

Overview: A cylindrical air-driven shock tube has been used to simulate blast overpressure (BOP) and study how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain. We have generally completed the work outlined in the progression of milestones for this project as was described in the previous annual reports. We requested a NCE continuation period to prepare reports and manuscripts, and to also replicate experiments using a recently acquired advanced blast simulator (ABS, fig 1) which provides a substantial refinement and improvement over the open-ended cylindrical shock tubes generally used for laboratory blast simulations. Working closely with Dave Ritzel, a blast physics expert, we became aware of several drawbacks of the cylindrical shock tube used for all experiments with this project to-date, which are universal for all open-ended cylindrical shock tubes; notably, in the absence of an end wave eliminator, the negative phase and

recompression waves are artefacts of the rarefaction from the end of the open tube and the secondary shock is moving in the reverse direction (upstream not downstream). Additionally, without a reflection eliminator, waves reverberate throughout the length of the tube after the passage of the initial shock front (Ritzel et al., 2011). Finally, rather than the sharp peak positive pressures associated with the Friedlander waveform, cylindrical shock tubes typically produce plateau waveforms with relatively long durations (6-12 msec).

With a divergent transition section and an end wave eliminator, the recently acquired ABS eliminates these artefacts along with the positional heterogeneity in pressures and flow conditions encountered in cylindrical shock tubes (Ritzel et al., 2011). In the ABS, positive pressure durations can be reduced to 1-2 msec, which may better represent waveforms resulting from IEDs. While the work on this project has been effectively completed using the cylindrical shock tube, we strongly believe that it is important to repeat several key experiments using the new ABS to confirm results, particularly since the flow conditions are quite different between the two devices (fig x) and the means by which rats were secured in the old shock tube and exposed to blast overpressure evolved substantially over the duration of the project as we became more aware of the impact of set-up variables on experimental measures and outcomes. Confirmation of results obtained with the cylindrical shock tube by blast simulations in the ABS will validate the findings and also provide valuable insights for their interpretation. As noted previously, bad blast simulations have confounded much of the preclinical biomedical blast literature to date, and we strongly desire to correct that situation.

Task 1: Using a compression-driven shock tube, measure, compare and correlate external (i.e. shock tube), systemic (i.e. vascular arterial and venous), and central (e.g. intracranial pressure) effects of BOP of varied intensities.

Flow conditions following membrane rupture in the cylindrical shock tube and the ABS have been closely compared and evaluated using inanimate objects before evaluating animal experimental subjects. As noted previously, the divergent transition section design of the ABS yields shock waves of shorter duration which are followed by a negative pressure and a secondary shock wave, which are characteristics of the Friedlander waveforms encountered in the open field that are not accurately reproduced in cylindrical shock tubes. Following extensive comparison of the pressure waveforms produced with different membrane materials and combinations of membrane materials along with and different gases used for pressurization, we devised a means to secure the test subject in the ABS which should minimize confounding influences seen with varied means of restraint (Goldstein et al., 2012). An animal use protocol based upon these test findings has been reviewed and approved by the WRAIR/NMRC IACUC and awaits approval by the MRMC ACURO. Within the month, we anticipate approval to transition to experimental animals to next evaluate systemic (i.e. vascular arterial and venous), and central (e.g. intracranial pressure) effects of BOP of varied intensities in the ABS in comparison to those seen in the cylindrical shock tube.

Task 2: Determine if measured pressure changes in the experimental subject are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures.

Since we did not yet have an IACUC- and ACURO-approved protocol for animal experiments using the ABS, we have not performed any additional animal exposures in this task. Using tissue samples previously prepared following BOP exposures in the cylindrical shock tube, we made additional neurochemical and neurobiological measurements.

Task 3: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and neurobehavioral outcome measures.

In the absence of an IACUC- and ACURO-approved protocol for animal experiments using the ABS, we have not done additional work with Kevlar vest evaluations during this reporting period. An animal use protocol has been reviewed and approved by the WRAIR/NMRC IACUC, which will allow us to do so shortly.

Task 4: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and acute cerebrovascular measurements.

In the absence of an IACUC- and ACURO-approved protocol for animal experiments using the ABS, we have not done additional work with Kevlar vest evaluations during this reporting period. An animal use protocol has been reviewed and approved by the WRAIR/NMRC IACUC, which will allow us to do so shortly.

KEY RESEARCH ACCOMPLISHMENTS

Bulleted list of key research accomplishments emanating from this research.

- BOP exposure conditions have been greatly refined to create a high fidelity simulation of blast TBI in the advanced blast simulator.
- Based upon discovery that BOP-induced acceleration and displacement potentially significantly contributed to the TBI injury mechanisms (and protective effects of vests) previously observed and characterized in the cylindrical shock tube, displacement/translation resulting from BOP has been carefully analyzed using inanimate objects in preparation for blast exposures of rodent test subjects in the ABS.
- Working from records collected previously from experimental subjects exposed to BOP in the cylindrical shock tube, EEG assessments have been further developed as a means of characterizing blast TBI and amelioration of blast TBI by protective vests.

REPORTABLE OUTCOMES

Provide a list of reportable outcomes that have resulted from this research to include:

Book Chapter:

Vogel, EW, Morrison B, Evilsizor MN, Griffiths DR, Thomas TC, Lifshitz, J, Sutton, RL, Long, JB, Ritzel, D, Lings, GSF, Huh, J, Raghupathi, R, McIntosh, TK. Experimental Models of Traumatic Brain Injury: Clinical Relevance and Shortcomings. In: "Cell Therapy for Neurologic Injury", C. Cox (ed). CRC Press, in press.

Based in part upon the work supported by this award, funding was sought through research preproposals and proposals submitted to the CDMRP and DMRP. Two proposals were selected for funding:

1. "Assessment and Treatment of Blast-Induced Auditory and Vestibular Injuries" was selected for funding as a Clinical Rehabilitative Medicine Research Program (CRM RP) Neurosensory Research Award within the Defense Health Program/Defense Medical Research Development Program.
2. "Elucidation of Inflammation Processes Exacerbating Neuronal Cell Damage to the Retina and Brain Visual Centers, as a Quest for Therapeutic Drug Targets, in a Rat Model of Blast Over Pressure Wave Exposure" was selected for funding as a CDMRP Clinical and Rehabilitative Medicine Research Program (CRM RP) Vision Research Program - Hypothesis Development Award.

CONCLUSION

An improved state-of-art high fidelity laboratory simulation of blast has been achieved using an advanced blast simulator (ABS) and pressure gauges record the static and dynamic pressures specifically occurring in the immediate environment of the experimental subject for each shockwave. From these measurements, wave velocity and dynamic pressure (blast wind) can be calculated. Following these essential characterizations, the ABS will now be used to validate findings made with a cylindrical shock tube in which intracranial and intravascular pressure recordings closely resembled ambient pressures and were unaltered by protective vests.

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- Ritzel, D.V., Parks, S.A., Roseveare, J., Rude, G. Sawyer, T., "Experimental Blast Simulation for Injury Studies", NATO/RTO HFM-207 Symposium, Halifax, Canada, 3-5 Oct 2011.

APPENDICES

1. SUPPORTING DATA

SUPPORTING DATA

During this reporting period, the 24 in diameter advanced blast simulator (ABS) was used to refine the experimental procedures to generate a high fidelity Friedlander waveforms closely resembling that produced by explosives in the open field. As noted previously, with its divergent transition section and end wave eliminator (identified as a dump tank in fig 1), the ABS waveforms contain a genuine negative pressure phase and a secondary shock (fig 2) in contrast to pressures recorded in cylindrical shock tubes (fig 3). Comparison of these pressure tracings highlights the contrast between the “Friedlander-like” sharp peak positive pressures produced in the ABS (fig 2) and the plateau waveforms with relatively long durations (6-12 msec) produced in this and other cylindrical shock tubes (fig 3), which will yield unscaled drag forces greatly exceeding those occurring with an explosion in the free field. In addition, the difference between the total and static pressure recordings (blue vs green tracings in figs 2 and 3) is much less in the ABS than in the cylindrical shock tube. This difference between total and static pressure is the dynamic pressure which gives rise to blast wind resulting from the kinetic energy imparted to the air as it is traversed by the shock wave. In addition to creating a higher fidelity shock wave, the ABS is equipped with optical windows and gauge ports which allow high speed video and pressure recordings to capture the flow conditions and response of the test subject (i.e. translation, acceleration, deformation, etc.).

Fig 2. ABS pressure trace

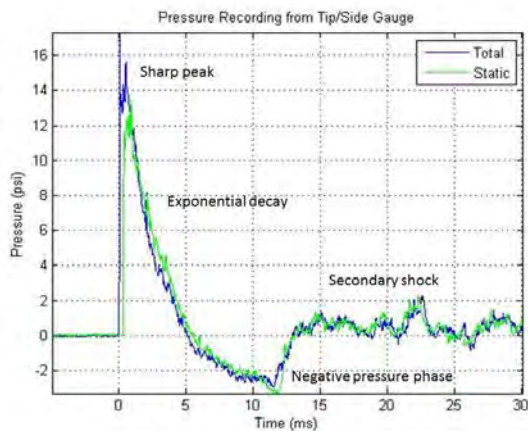


Fig 3. Cylindrical shock tube pressure trace

